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ORIGINAL ARTICLE

Haematological response and overall survival in two consecutive Dutch patient cohorts with AL amyloidosis diagnosed between 2008 and 2016

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ABSTRACT

Background: Although survival has improved in recent decades, the short-term prognosis of patients with immunoglobulin light chain (AL) amyloidosis remains grim. We aimed to assess overall survival (OS) of AL amyloidosis patients by comparing cohorts in two consecutive time periods.

Methods: Data were collected and compared on 126 patients from two tertiary referral centres in The Netherlands during the time periods 2008–2012 and 2013–2016.

Results: There was a non-significant trend to improved 6-month OS in the last cohort (78% vs. 67%, $p = .216$, crude odds ratio 1.66, 95%CI 0.74–3.70, adjusted odds ratio 2.22, 95%CI 0.88–5.56). Patients in this cohort had higher Mayo risk scores (stage III 40% vs. 24%, $p < .001$ and revised stage IV 14% vs. 11%, $p < .001$), higher use of bortezomib (50% vs. 30%), and better haematological response (complete response/very good partial response in 39% vs. 27%, $p < .001$). Diagnostic delay was similar in both time periods.

Conclusions: In the 2013–2016 cohort there was a trend toward improved 6-month OS, and an improved haematological response. Patients in this cohort had more advanced cardiac disease and received bortezomib more frequently, but diagnostic delay was similar to the 2008–2012 cohort. For further prognostic improvement, practitioners should be more alert, especially for cardiac amyloidosis.

Abbreviations: AL: amyloid light chain; ASCT: autologous stem cell transplantation; BMPC: bone marrow plasma cells; BNP: B-type natriuretic peptide; CR: complete response; dFLC: difference between involved and uninvolved free light chains; FLC: free light chains; HDM: high dose melphalan; IMiD's: immunomodulatory imide drugs; NT-proBNP: N-terminal proBNP; OS: overall survival; PR: partial response; SD: stable disease; UMC: University Medical Centre; VGPR: very good partial response

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AL amyloidosis; survival; prognosis; time trend

Introduction

Systemic immunoglobulin light chain (AL) amyloidosis is characterized by aggregation and deposition of monoclonal immunoglobulin free light chains (FLC) in several tissues, leading to organ dysfunction. Clinical manifestations and outcomes depend on the extent of organ involvement. Cardiac involvement in particular has a major negative impact on prognosis. Another negative prognostic factor is a delay between start of symptoms and the diagnosis, because these patients present with more advanced organ damage [1–3].

The short-term prognosis of AL amyloidosis depends greatly on the extent of cardiac involvement. Biomarkers of heart failure and cardiac injury, such as B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP) and troponins T or I are therefore used for risk assessment and monitoring. The long-term prognosis of patients with AL amyloidosis depends on haematological response after treatment and on overall organ involvement. The latter is related to the on-going supply of involved FLCs to the tissues. Consequently, serum FLCs, and especially the difference between the involved and uninvolved FLC (dFLC), can also be used for risk assessment and monitoring [4–6].

Therapy used for the treatment of multiple myeloma has been shown to be effective in AL amyloidosis as well [7]. New developments in treatment modalities for multiple myeloma have also changed treatment of the far less common AL amyloidosis [8]. The introduction of high dose melphalan (HDM) followed by autologous stem cell transplantation (ASCT) led to a better haematological response and organ response in AL amyloidosis patients [9]. Over the years, the treatment-related mortality of this procedure has declined, likely due to better patient selection [10]. However, most patients are not eligible for ASCT. Recently, proteasome inhibitors such as bortezomib and immunomodulatory imide drugs (IMiD's) such as thalidomide and lenalidomide have become available [7,11]. A recently published study conducted in the Mayo Clinic

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showed that the introduction of melphalan-dexamethasone and bortezomib-based therapy as first-line therapy has contributed to improved overall survival (OS). This study, which included 1551 patients, showed an improvement of the short-term prognosis: 6 month OS increased from 63% in cohort 2000–2004 to 76% in cohort 2010–2014 ($p < .001$). Nevertheless, short-term mortality remained high [11].

Until the 1980s, survival of patients with AL amyloidosis in the Netherlands was very poor, with a median OS of 7 months. This was primarily because the vast majority of patients had been left untreated [12]. This improved to a median OS of 12 months in patients diagnosed between 1990 and 2003, who were treated with prednisone and melphalan or HDM followed by ASCT [13]. However, more recent outcomes of patients with systemic AL amyloidosis in the Netherlands are unknown. We therefore evaluated 126 AL amyloidosis patients who were diagnosed between 2008 and 2016 in two tertiary referral centres for amyloidosis in the Netherlands, and compared the last cohort (2013–2016) with the first cohort (2008–2012).

Methods

Patients

We retrieved information on 186 patients who were diagnosed with systemic AL amyloidosis at the University Medical Centre Utrecht (UMC Utrecht) and the University Medical Centre Groningen (UMC Groningen). At the UMC Groningen the registry started in 2008 and at the UMC Utrecht in 2012. Patients were eligible for inclusion if diagnosed with systemic AL amyloidosis and treated at either centre between January 1 2008 and December 31 2016. Of the 186 patients, 48 patients were not eligible because they fell outside the scope of our study: seven patients were diagnosed in an earlier time period; in five patients the diagnosis of amyloidosis was uncertain; 35 patients were seen for a second opinion and were treated elsewhere; and one patient who received stem cell therapy was sent back immediately afterwards to the referring hospital. Of the remaining 138 eligible patients with AL amyloidosis, 12 (8.7%) were lost to follow-up, thus leaving 126 patients for analysis. We divided these patients into two cohorts based on the year of diagnosis; 2008–2012 (cohort I) including 46 patients, and period 2013–2016 (cohort II) including 80 patients.

In all included cases, amyloidosis was diagnosed by positive Congo red staining of tissue retrieved using a screening fat tissue aspirate or targeted organ biopsy. Systemic involvement was confirmed by another biopsy from a different organ or tissue, or by the combination of clinical features typical for amyloidosis in an organ or tissue other than that from which a biopsy with a positive Congo red stain was obtained. Amyloid type AL was preferably demonstrated by a positive anti-kappa or anti-lambda light chain staining using immunohistochemistry in combination with a definitely negative staining for amyloid type amyloid A (AA) and amyloid transthyretin (ATTR). In addition, increased production of either kappa or lambda FLC had to be present. Diagnostic delay was defined as the time between the first documented signs or symptoms of AL amyloidosis and the date that amyloid had been diagnosed by biopsy. Both organ involvement and haematological response were based on consensus criteria [6,14]. Haematological response categories are complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD) and progression. At UMC Utrecht, the cardiac biomarkers BNP and troponin I were measured, while at UMC Groningen, NT-proBNP and troponin T were used. Based on these cardiac biomarkers, both the Mayo 2004 and 2012 staging system criteria were applied [4,5]. For bone marrow plasma cell percentage, the highest estimated percentage was used. Treatment was categorized as ASCT after high-dose or intermediate-dose melphalan, melphalan-dexamethasone (MDex), bortezomib-based regimen, IMiD-based regimen, single-agent dexamethasone or "other treatment". The latter category included treatment commonly used for Waldenström's macroglobulinemia: rituximab monotherapy or rituximab in combination with chlorambucil or dexamethasone and cyclophosphamide.

Data analysis

The χ^2 test was used to compare differences between nominal and ordinal variables, and the one-sample *t*-test and the independent-samples *t*-test were used to compare means between groups. Kaplan–Meier analysis was used for survival analysis. Besides our own data, in the analysis we used historical data on overall survival of systemic amyloidosis previously reported in The Netherlands [12,13]. Only patients with AL amyloidosis were included in the analysis. OS was calculated using time from diagnosis to last follow-up or death. Due to the short follow-up in the most recent cohort, median OS was not expected to be reached. In addition we determined 6-month OS and 2-year OS. The 6-month follow-up was available for all patients, but the 2-year follow-up only for 25% of patients. The majority of these missing data points were from the 2013-2016 cohort, because the 2 year follow-up of part of this cohort has not yet taken place. To compare the 6-month OS of the two cohorts (2008–2012 vs. 2013–2016), we used a multivariate analysis in line with a previous study [11], with adjustment for age, gender and variables related to severity of disease (dFLC, number of bone marrow plasma cells (BMPC), number of organs involved and heart involvement). To deal with missing values (six for dFLC and 14 for BMPC) we did multiple imputation (5 times) before multivariate analysis and used pooled estimated adjusted odds ratios with 95% confidence intervals. Because data from UMC Utrecht was only available from 2012 onwards, we performed sensitivity analysis comparing the results from UMC Utrecht and UMC Groningen selectively from 2012 to 2016. Analyses were performed with SPSS version 23.

Results

Baseline characteristics

The baseline characteristics are shown in Table 1. The mean age at diagnosis was 64 years (range 45–82) and 57% of the

Table 1. Baseline characteristics of 126 AL amyloidosis patients, divided into two consecutive time periods.

Characteristic	Both time periods ($n = 126$)	Period 2008–2012 ($n = 46$)	Period 2013–2016 ($n = 80$)	p value
Mean age in years	63.9	64.1	63.8	.469
Age $\geq$ 65 years, *n* (%)	60 (48)	22 (48)	38 (48)	.972
Male, n (%)	72 (57)	27 (59)	45 (56)	.789
Organs involved, *n* (%)				
>2 organs	57 (45)	18 (39)	39 (49)	.296
Neurological	46 (37)	15 (33)	31 (39)	.491
Heart	93 (74)	34 (74)	59 (74)	.984
Liver	26 (21)	6 (13)	20 (25)	.061
Renal	78 (62)	27 (59)	51 (64)	.813
Gastro-intestinal tract	33 (26)	12 (26)	21 (26)	.984
Lung	6 (5)	3 (7)	3 (4)	.482
Soft tissue	33 (26)	13 (28)	20 (25)	.689
Light chains				
λ restricted, *n* (%)	90 (71)	33 (72)	57 (71)	.747
Unknown	*1*	*0*	*1*	
Median dFLC in mg/dL	17.5	16.9	18.2	**.008**
Unknown	*6*	*0*	*6*	
dFLC <0.5 mg/dL, *n* (%)	3 (2)	0 (0)	3 (4)	.062
dFLC $\geq$ 18 mg/dL, *n* (%)	59 (49)	22 (48)	37 (46)	.159
Mean BMPC in %	13.5	15.0	12.5	.107
Unknown	*14*	*1*	*13*	
Brain natriuretic peptides				
Unknown	*8*	*2*	*6*	
Median NT-proBNP in ng/L	2100.5	2462.0	2100.5	.402
NT-proBNP $\geq$ 332 ng/L, n (%)	84 (82)	35 (46)	49 (61)	.079
NT-proBNP $\geq$ 1800 ng/L, *n* (%)	54 (53)	21 (46)	33 (41)	.071
BNP median, pg/mL	745	487.0	1139.0	.236
BNP $\geq$ 100 pg/mL, *n* (%)	23 (88)	4 (9)	19 (24)	**.036**
Troponins				
Unknown	*19*	*4*	*15*	
Troponin I median, ng/L	0.04	0.00	0.05	.306
Troponin I $\geq$ 0,10 μg/L, *n* (%)	7 (29)	0 (0)	7 (9)	**.045**
Troponin T median, μg/L	0.032	0.00	0.048	.665
Troponin T $\geq$ 0,035 μg/L, *n* (%)	38 (46)	11 (24)	27 (34)	**<.001**
Troponin T $\geq$ 0.025 μg/L, *n* (%)	46 (55)	13 (28)	33 (41)	**<.001**
Mayo AL amyloidosis 2004 stage, % I/II/III/unknown	11/29/34/25	15/50/24/11	9/18/40/34	**<.001**
Mayo AL amyloidosis 2012 stage, % I/II/III/IV/unknown	14/14/22/13/37	24/24/24/11/17	9/9/21/14/48	**.002**

dFLC: difference between the involved and uninvolved free light chains; BMPC: bone marrow plasma cells; BNP: B-type natriuretic peptides; NT-proBNP: N-terminal proBNP. A p-value < 0.05 is considered bold significant.

patients were male. The mean time from start of complaints to diagnosis was 14.7 months (range 0–156 months). This delay did not decrease as the study progressed and was 14.0 months in cohort I versus 14.9 in cohort II ($p = .947$). The most common symptoms at diagnosis were oedema (43.7%), dyspnoea (42.9%), fatigue (38.9%), weight loss (33.3%), peripheral sensory neuropathy (27.0%), changed defaecation pattern (22.2%), orthostatic hypotension (19.8%) and bleeding tendency (15.1%). Four patients did not have any complaints at diagnosis. The percentage of patients with two or more organs involved did not differ between the two cohorts and was 49% in cohort II and 39% in cohort I ($p = .491$). Cardiac involvement was seen in 74% of patients in both cohorts.

Lambda restricted light chains were found in 71% of the patients and in 4 patients (5%) the light chain amyloidosis was associated with Waldenström's disease. The median dFLC was significantly higher in cohort II (16.9 mg/dL in cohort I and 18.2 mg/dL in cohort II, $p = .008$). There was no significant difference in mean BMPC percentage between the cohorts (15% in cohort I and 12.5% in cohort II, $p = .107$).

The cardiac biomarkers NT-proBNP, BNP, troponin I and T were not always available in the data. As a result, only 75% of the patients were staged by the Mayo 2004 staging system [4] and 63% by the revised Mayo 2012 staging system [5]. More patients had poorer prognoses in cohort II; 40% of patients from cohort II were in Mayo stage III compared to 24% from cohort I ($p < .001$), while 14% from cohort II were in revised Mayo stage IV compared to 11% from cohort I ($p < .001$). Based on only highly elevated NT-proBNP of >8500 ng/L, 13 patients in cohort I and 14 patients in cohort II ($p = .055$) were classified as very high-risk patients.

Treatment

In total, 109 patients (87%) were treated. The other 13% of the patients did not receive treatment due to advanced disease or death before start of treatment. Patients received up to five lines of treatment with a median of one line. In total, 48 different combinations of regimens were used as first-line therapy and were grouped into five categories, which are shown in Table 2. In the first line of treatment, the use of bortezomib-based therapy increased from 30% in cohort I to 50% in cohort II, whereas the use of IMiD-based therapy decreased from 30% to 8%.

Table 2. Treatment and haematological response of 126 AL amyloidosis patients, divided into two consecutive time periods.

Characteristic	Both time periods ($n = 126$)	Time period 2008–2012 ($n = 46$)	Time period 2013–2016 ($n = 80$)	p value	
First line of treatment, *n* (%)					
ASCT	25 (20)	9 (20)	16 (20)	**.045**	
MDex	3 (2)	1 (2)	2 (3)		
Bortezomib-based	54 (43)	14 (30)	40 (50)		
IMiD-based	20 (16)	14 (30)	6 (8)		
- Lenalidomide	8 (6)	2 (4)	6 (8)		
- Thalidomide	12 (10)	11 (24)	1 (1)		
Single-agent dexamethasone	2 (2)	0 (0)	2 (3)		
Others	5 (4)	2 (4)	2 (3)		
No treatment	17 (13)	6 (13)	11 (14)		
Haematological response to first line treatment (*n*= 110) (%)					
Complete response	24 (22)	8 (20)	16 (23)	**<.001**	.563
Very good partial response	14 (13)	3 (7)	11 (16)		
Partial response	22 (20)	9 (22)	13 (19)	–	
Stable disease	17 (15)	8 (20)	9 (13)		
Progression	4 (4)	3 (7)	1 (1)		
Unknown	29 (26)	10 (24)	19 (28)		

ASCT: autologous stem cell transplantation; MDex: melphalan dexamethasone; IMiD: immunomodulatory imide drugs.

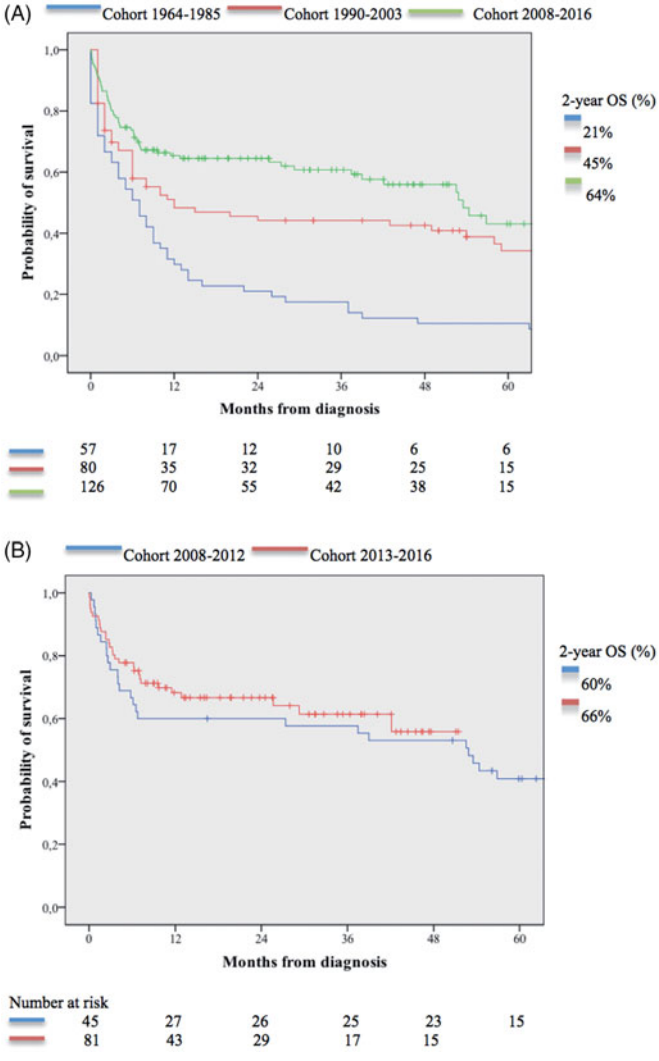

Figure 1. Survival from time of diagnosis per cohort. (A)Survival of historical cohorts 1964–1985 12 and 1990–2003 13 versus complete current study cohort 2008–2016, $p < .001$. (B) Survival of cohort 2008–2012 versus cohort 2013–2016, $p = .503$.

Overall, 25 patients (20%) received ASCT as first line of treatment in both cohorts. In 23 out of 25 patients, ASCT was preceded by induction therapy. In cohort I, ASCT was preceded by IMiD-based induction therapy in 50% of the patients and by bortezomib-based induction therapy in 30% of the patients. In cohort II, IMiD-based induction therapy was used in 23% of patients and bortezomib-based induction therapy in 75%.

Haematological response

The haematological response to first line of treatment improved between the cohorts; CR/VGPR was reached in 27% in cohort I and 39% in cohort II ($p < .001$). In patients who received ASCT, the percentage of patients who achieved VGPR or CR was similar in both cohorts: 70% in cohort I and 65% in cohort II ($p = .521$). Haematological response data to first line of treatment was missing for 24% of patients in cohort I and 28% in cohort II.

Survival

OS in our study was compared to survival in previous studies reported in The Netherlands (Figure 1(A)). The median OS significantly improved over time: from 7 months in patients diagnosed between 1964–1985 to 12 months in patients diagnosed between 1990–2003 and to 53.5 months in patients in our study who were diagnosed between 2008–2016 ($p < .001$) [12,13].

The median OS was 52.5 months for cohort I and 53.5 months for cohort II ($p = .503$). The 6-month OS was 67% for cohort I and 78% for cohort II (OR 1.66 (95% CI 0.74–3.70), $p = .216$) and the 2-year OS was 60% for cohort I and 66% for cohort II ($p = .349$). Survival by cohort is shown in Figure 1(B). This OS curve suggests trend (non-significant) towards improved survival in the most recent cohort. The multivariate analysis for factors influencing 6-month survival is shown in Table 3. After adjustment for number of organs involved, heart involvement, dFLC and BMPCs, the trend to improved survival remained, with a higher point estimate (OR 2.22, 95% CI 0.88–5.56, $p = .09$).

Median OS was much higher in patients without cardiac involvement (median OS was not reached in patients without cardiac involvement compared to 42.1 months for patients with cardiac involvement, $p = .005$). This was also seen in the 6-

Table 3. Two models with adjusted odds ratios (OR) for 6-month overall survival in 126 AL amyloidosis patients.

	Model 1 Adjusted OR (95% CI)	*p* value	Model 2 Adjusted OR (95% CI)	*p* value
Cohort 2013-2016	2.17 (0.85–5.56)	.106	2.22 (0.88–5.56)	.091
Heart involvement	0.16 (0.03–0.78)	.023	0.17 (0.04–0.81)	.026
≥2 organs involved	0.42 (0.17–1.08)	.069	0.43 (0.17–1.09)	.074
BMPC ≥ 10%	0.99 (0.97–1.00)	.102	0.99 (0.97–1.00)	.100
dFLC per mg/dL	1.00 (0.99–1.00)	.100	1.00 (0.99–1.00)	.133
Age per year	0.97 (0.92–1.02)	.256	–	–
Female gender	0.74 (0.29–1.85)	.512	–	–

95% CI: 95% confidence interval; OR: odds ratio.
Cohort 2013–2016 was compared to cohort 2008–2012. The unadjusted or crude odds ratio was 1.66 (95% CI 0.74–3.70). When adjusted for age, gender and variables related to severity of disease mentioned in Table 3, the odds ratio increased to 2.17 (95% CI 0.85–5.56) and when adjusted only for variables related to severity of disease, the odds ratio further increased to 2.22 (95% CI 0.88–5.56).

month OS (94% without cardiac involvement compared to 66% with cardiac involvement, $p = .004$) and the 2-year OS (87% compared to 56%, $p = .002$). The survival curve of patients with and without cardiac involvement in both cohorts is shown in Figure 2(A). A trend to improved survival was seen in patients presenting with fewer than two organs involved (median OS of 56.8 months with fewer than 2 organs involved compared to 39.0 months with 2 or more organs involved, $p = .075$); 6-month OS, 81% compared to 66%, $p = .047$; 2-year OS, 73% compared to 54%, $p = .028$). The median OS was higher in patients with dFLC <18 mg/dL than in patients with dFLC ≥18 mg/dL (median OS was not reached in patients with dFLC <18 mg/dL compared to a median OS of 11.47 months in patients with dFLC >18 mg/dL, $p = .002$), 6-month OS 82% compared to 64% ($p = .03$) and 2-year OS 78% compared to 49% ($p < .001$). The survival curve of patients according to dFLC cut-off 18 mg/dL is shown in Figure 2(B). The Mayo 2004 and 2012 staging systems were both prognostic for OS. The 6-month OS for patients with Mayo 2004 risk score I was 100%, with II it was 78% and with III it was 53% ($p < .001$); the 2-year OS for patients with these risk scores was 92%, 73% and 38% ($p < .001$), respectively. The 6-month OS for patients with Mayo 2012 risk score I was 94%, with II it was 89%, with III it was 57% and with IV it was 38%. The 2-year OS for patients with these risk scores was 89%, 82%, 49% and 31% ($p = .002$), respectively. The OS was also dependent on the type of therapy patients received ($p < .001$). In patients who received ASCT as the first line of treatment, 6-month OS was 100% and 2-year OS was 91%. For patients who received non-ASCT therapy, the median OS was 52.9 months, the 6-month OS was 75% and the 2-year OS was 67%. For the 13% of patients who did not receive any treatment, the median OS was 2.4 months, the 6-month OS was 29% and the 2-year OS was 10%.

Sensitivity analysis comparing results of the UMC Utrecht and the UMC Groningen

The 6-month OS was 83% (25/30) at UMC Utrecht and 69% (45/65) at UMC Groningen. The 2-year OS was 67% (20/30) at UMC Utrecht and 63% (41/65) at UMC Groningen. A CR or VGPR in this time period was reached in 59.1% of the patients at UMC Utrecht and 47.2% at UMC Groningen ($p = .38$). Differences between the two centres in OS and haematological response were not significant.

Discussion

In this retrospective analysis of 126 AL amyloidosis patients diagnosed and treated in the two expertise centres in The Netherlands, we evaluated presentation, diagnostic delay, treatment and outcome between 2008 and 2016 and compared two patients cohorts (2008–2012 and 2013–2016).

The time between symptom onset and diagnosis was similar in the two cohorts, with a median diagnostic delay of 15 months. This is similar to the results of a recent patient survey, with a delay in diagnosis of more than one year in 37.1% of the patients [15]. This median delay in diagnosis is longer than previously reported. The Mayo Clinic reported a delay of 10 months, an Italian study reported 6 months, and a Chinese study reported 7 months [11,16,17]. Early diagnosis is crucial; it enables early treatment intervention and may therefore prevent irreversible organ damage and improve the prognosis [16]. Lousada et al. stated that only 7.6% of the patients received the diagnosis of amyloidosis after visiting one physician, and that 31.8% visited ≥5 physicians before receiving the diagnosis [15]. This suggests that the diagnosis of AL amyloidosis should be considered more often by cardiologists, nephrologists, neurologists and haemato-oncologists. Although initiatives were undertaken in the Netherlands to improve awareness among both lay people and physicians to reduce diagnostic delay, such as the launch of a patient organization in 2013 and the initiation of expert centres in 2015, these efforts have not yet resulted in greater awareness and earlier diagnosis. Therefore, improving the awareness of medical specialists should still have high priority.

The total rate of cardiac involvement was similar in both cohorts (74%), and was in line with other cohort studies that reported rates between 53 and 76% [11,17,18]. Surprisingly, patients in the more recent cohort had even more advanced cardiac disease with higher Mayo 2004 and 2012 risk scores. Moreover, in the more recent cohort a higher (but not significantly higher) proportion of the patients presented with two or more organs involved. Also, the median dFLC was significantly higher in the more recent cohort (18.2 mg/dL versus 16.9 mg/dL). This dFLC value is another important prognostic factor, and is lower than that reported in a study from the Mayo Clinic: a dFLC of 23.7 mg/dL [11].

It should be noted that our study was based on patients referred to tertiary centres. Compared to other studies,

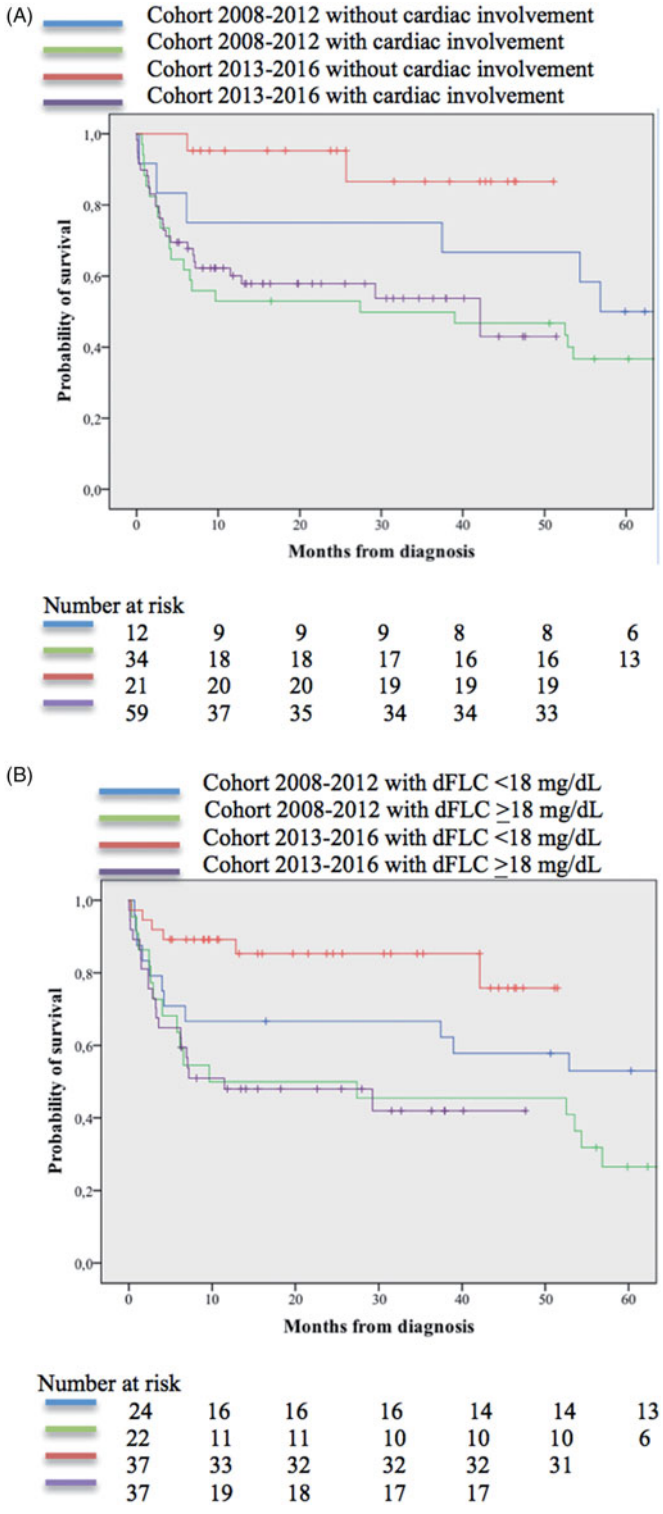

Figure 2. Survival of subgroups in all 126 AL amyloidosis patients. (A) Cardiac involvement versus no cardiac involvement in cohort I and II, $p < .025$. (B) Difference between the involved and uninvolved free light chain <18 mg/dL or >18 mg/dL in cohort I and II, $p = .003$.

patients with more advanced disease may therefore be over-represented. In a 2012 Swedish nationwide registration study, the estimated incidence of AL amyloidosis was 3.2 per million inhabitants [19]. In The Netherlands, comprising 17 million inhabitants, 55 newly-diagnosed patients with AL amyloidosis per year would then be expected. In two of our expertise centres, 186 patients were seen during 9 years, or about 20 new patients per year on average. We therefore analyzed approximately 40% of all cases of AL amyloidosis in the Netherlands that were diagnosed from 2008 to 2016.

A factor that could have affected our study concerns the new treatment options that have become available in recent decades. In our study population, 13% of the patients did not receive any treatment due to advanced disease or death before start of treatment. This is a higher percentage than previously reported in a study by the Mayo Clinic, in which 6%, 7% and 11% of the patients remained untreated in the time periods 2000–2004, 2005–2009 and 2010–2014 respectively [11]. In our study and others reported in literature, in recent time periods patients received bortezomib-based therapy more often as first line treatment in the more recent time periods [11] and in recent years induction therapy changed from IMiD-based therapy to bortezomib-based therapy. Importantly, these new treatment options led to significantly improved haematological response in our study. In patients who received first line treatment, the CR/VGPR rate was 27% in the 2008–2012 cohort and 39% in the 2013–2016 cohort. In a retrospective study at the Mayo Clinic, a much higher CR/VGPR rate was reported (51% in 2000–2004, 58% in 2005–2009 and 66% in 2010–2014). This could be partly explained by the higher ASCT rate in this selected Mayo cohort, which was about one-third compared to 20% in our cohort. In the Mayo cohort, patients who received ASCT had the highest response rate (65% to 70%) and this figure remained stable during the time period studied [11]. As reported by D'Souza et al., not only haematological response after ASCT improved over the years, but early mortality after ASCT also declined between 1995 and 2012 [20].

In our analyses, a non-significant trend to improved 6-month OS was seen in the more recent cohort (67% in the 2008–2012 cohort and 78% in the 2013–2016 cohort). The point estimate of this trend was even better after adjustment for variables related to severity of disease (dFLC, BMPCs, number of organs involved and heart involvement) (crude OR 1.66, 95% CI 0.74–3.70, adjusted OR 2.22, 95% CI 0.88–5.56). This effect is very likely the result of more effective treatment over the years, even though patients in the more recent cohort have more severe disease (higher Mayo risk scores and dFLC). In line with our results, study at the Mayo Clinic showed a statistically significant improvement in 6-month OS from 63% in the 2000–2004 cohort to 76% in the 2010–2014 cohort [11].

Strengths and limitations

We analyzed treatment data for approximately 40% of the total AL amyloidosis population in The Netherlands, that was diagnosed between 2008 and 2016.

Limitations: In our study, 8.7% of patietns were lost to follow up and we had missing values in some determinants and in haematological response as shown in Table I. If missing values in haematological response data occured for different reasons in one cohort compared to the other and/or were not completely random, this could bias the results by either overestimating or underestimating the effect. Both of

the above shortcomings are related to the use of routine care data. Another limitation concerns patient follow-up. Although all patients had 6 months of follow up, a majority (75%) had not yet completed two years of follow-up. Data on 2-year OS should therefore be interpreted cautiously. Finally, limitations are the retrospective nature of the study and the relatively low number of outcomes.

Conclusion

By comparing the 2008–2012 and 2013–2016 cohorts we showed an improvement in haematological response of AL amyloidosis patients within the last decade. There was also a trend towards improved 6-month OS. These favourable findings are probably the result of improvements in anti plasma cell treatment over the years. However, the delay in diagnosis is still too high and patients in the most recent cohort even presented with more advanced disease and worse risk scores. To reduce the long diagnostic delay that currently blocks further improvement in survival, awareness of amyloidosis should be improved among cardiologists, nephrologists, neurologists and other medical specialists.

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Disclosure statement

The authors report no conflicts of interest.

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References

[1] Falk RH, Alexander KM, Liao R, et al. AL (light-chain) cardiac amyloidosis: a review of diagnosis and therapy. J Am Coll Cardiol. 2016;68:1323–1341.
[2] Muchtar E, Buadi FK, Dispenzieri A, et al. Immunoglobulin light chain amyloidosis from basics to new developments in diagnosis, prognosis and therapy. Acta Haematol. 2016;135:172–190.
[3] Palladini G, Merlini G. What is new in diagnosis and management of light chain amyloidosis? Blood. 2016;128:159–168.
[4] Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. JCO. 2004;22:3751–3757.
[5] Kumar S, Dispenzieri A, Lacy MQ, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. JCO. 2012;30:989–995.
[6] Comenzo RL, Reece D, Palladini G, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. Leukemia. 2012;26:2317–2325.
[7] Weber N, Mollee P, Augustson B, et al. Management of systemic AL amyloidosis: recommendations of the Myeloma Foundation of Australia Medical and Scientific Advisory Group. Intern Med J. 2015;45:371–382.
[8] Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet. 2016;387:2641–2654.
[9] Hazenberg B, Croockewit A, Holt B, et al. Extended follow up of high-dose melphalan and autologous stem cell transplantation after vincristine, doxorubicin, dexamethasone induction in amyloid light chain amyloidosis of the prospective phase ii HOVON-41 study by the Dutch-Belgian co-operative trial group for hematology oncology. Haematologica. 2015;100:677–682.
[10] Gertz MA. Immunoglobulin light chain amyloidosis: 2016 update on diagnosis, prognosis, and treatment. Am J Hematol. 2016;91:947–956.
[11] Muchtar E, Gertz MA, Kumar SK, et al. Improved outcomes for newly diagnosed AL amyloidosis between 2000 and 2014: cracking the glass ceiling of early death. Blood. 2017;129:2111–2119.
[12] Janssen S, Van Rijswijk MH, Meijer S, et al. Systemic amyloidosis: a clinical survey of 144 cases. Neth J Med. 1986;29:376–385.
[13] Hazenberg B, van Rijswijk MH, Lub-de Hooge MN, et al. Diagnostic performance and prognostic value of extravascular retention of 123I-labeled serum amyloid P component in systemic amyloidosis. J Nucl Med. 2007;48:865–872.
[14] Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18–22 April 2004. Am J Hematol. 2005;79:319–328.
[15] Lousada I, Comenzo R, Landau H, et al. Light chain amyloidosis: patient experience survey from the amyloidosis research consortium. Adv Ther. 2015;32:920–928.
[16] Palladini G, Kyle RA, Larson DR, et al. Multicentre versus single centre approach to rare diseases the model of systemic light chain amyloidosis. Amyloid. 2005;12:120–126.
[17] Huang XH, Liu ZH. The clinical presentation and management of systemic light chain amyloidosis in China. Kidney Dis. 2016;2:1–9.
[18] Sanchorawala V, Wright DG, Seldin DC, et al. High-dose melphalan and autologous peripheral blood stem cell transplantation in AL amyloidosis: results of a prospective randomized trial. Bone Marrow Transplant. 2004;33:381–388.
[19] Hemminki K, Li X, Försti A, et al. Incidence and survival in non-hereditary amyloidosis in Sweden. BMC Public Health. 2012;12:974.
[20] D'Souza A, Dispenzieri A, Wirk B, et al. Improved outcomes after autologous hematopoietic cell transplantation for light chain amyloidosis: a center for international blood and marrow transplant research study. JCO. 2015;33:3741–3749.